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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HOLLERAN, ANNE L.	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,123	ERICKSON ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-6 and 8-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6 and 8-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/4/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment received Dec. 10, 2003 is acknowledged. Claims 1, 14 and 26 were amended.

Claims 1, 2, 4-6, and 8-48 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. In view of the papers received Dec. 10, 2003, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by the addition of inventor Walter Blattler.

A corrected filing receipt will be mailed by the PTO.

4. References 36 – 94 have been considered.

Claim Rejections Withdrawn:

5. The rejections of the claimed inventions over the prior art are withdrawn in upon consideration new grounds of rejection.

New Grounds of Rejection:

6. Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in view of Hudziak (U.S. Patent 5,725,856; issued Mar. 10, 1998; effective filing date Jan. 12, 1988) and further in view of Lewis (Lewis, G.D. et al, Cancer Immunol. Immunother. 37: 255-263, 1993; cited in the IDS).

In the broadest embodiment, the claimed inventions are drawn to methods of treatment of a tumor in a mammal, comprising determing that said tumor is characterized by the overexpression of an ErbB2 receptor, determining that said tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody, and administering to the mammal a thereapeutically effective amount of a conjugate of the ant-ErbB2 antibody with a maytansinoid.

Chari claims methods of treating cancer, comprising administering to a patient in need thereof, of an effective dose of a composition comprising one or more maytansinoids linked to a monoclonal antibody or a fragment, where the monoclonal antibody is selective for tumor cell antigens (see claim 1, col. 27). Chari discloses methods of killing selected cell populations comprising contacting a cell population or tissue suspected of containing cells from said selected cell population with a cytotoxic amount of one or more maytansinoids linked to a cell binding agent (col. 4, lines 8-14), and where the maytansinoid is a maytansine of claim 22 (see Fig. 1a and col. 8, lines 32-54), where the maytansinoid is maytansinol of claim 23 (see col. 7, lines 11-35), where the maytansinoid is a maytansinol ester of claim 24 (see col. 7, lines 11-35), where the maytansinoid is a C-3 ester of maytansinol of claim 25 (see col. 6, lines 17-25), where the maytansinoid is DM1 of claim 26 (see col. 8, lines 32 – 54). Chari teaches conjugates that

comprise 1 to 10 maytansinoids (encompassing claims 32 and 33; see col. 12, line 26-28) and teaches a conjugate that comprises 3 to 6 maytansinoids (col. 25, lines 5-35). Chari teaches some of the specific fragments of antibodies of claims 20 and 21, such as Fab, Fab', $F(ab)_2$ (col. 10, lines 5-7). Chari teaches linking by a disulfide group of claim 29 and 30 (col. 6, line 34) and other linkers as set forth in claims 27-30 (col. 21, line 16 – col. 23, line 40). Chari teaches treating cancer such as lung, breast, colon, prostate, kidney, pancreas, ovary and lymphatic cancer as in claims 9 and 10 (col. 14, lines 12-17).

Chari fails to teach conjugates comprising an antibody that binds to ErbB2, or comprising an antibody that binds to ErbB2, wherein the antibody is growth inhibitory, or induces cell death. Chari fails to teach immunoconjugates comprising the monoclonal antibody 4D5 (ATCC CRL 10463), or a humanized version of the monoclonal antibody 4D5 (ATCC CRL 10463). Chari fails to teach treatment of breast cancer that overexpresses ErbB2 at the 2+ or 3+ level.

However, Hudziak teaches methods of treating cancer comprising administering anti ErbB2 antibodies conjugated to cytotoxic agents (col. 9, line 56 – col. 10, line15 and col. 11, lines 32-45). In particular, Hudziak teaches the use of "immunotoxins", which are anti-ErbB2 antibodies that have been conjugated to cytotoxic molecules, for the purpose of delivering the cytotoxic molecule to an erbB2-expressing tumor. Hudziak teaches an anti-ErbB2 antibody that is a growth inhibitory antibody as in claim 4 (col. 18 – col. 19), and Hudziak teaches an anti-ErbB2 antibody that is cytotoxic as in claim 5 (col. 5, lines 54-57). Hudziak teaches the monoclonal antibody 4D5 (ATCC CRL 1463) encompassed by claims 14-16 (col. 18, lines 13-16) and a humanized antibody of claim 17 (col. 9, lines 24-39). Hudziak teaches that the antibody may be an antibody fragment (col. 10, lines 14-15). Hudziak teaches specific linkers

(col. 10, lines 3-14). Hudziak teaches methods for determining the level of over expression of ErbB2 in a tumor (col. 13, ines7-25). Hudziak teaches that ErbB2 (Her-2) is amplified or overexpressed in many human malignancies (col. 2, lines 38-64).

In addition, Hudziak teaches that for therapeutic methods the characteristics of the immunotoxin in combination with the characteristics of the patient and patient history will be used to determine a dose and a dose regimen (see col. 11, lines 32-45). Hudziak fails to specifically teach that one characteristic of the patient or patient history will be that the patient has not responded or responded poorly to an unconjugated anti-ErbB2 antibody. However, Lewis teaches that some tumor cells that overexpress ErbB2 fail to respond to murine monoclonal antibody 4D5 by exhibiting growth inhibition (see page 261, 2nd col. To page 262, 1st col.).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Chari and of Hudziak to make an immunotoxin for the purpose of treating patients having tumors that overexpress ErbB2. In view of the teachings of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid. In view of the fact that Hudziak clearly contemplated the use of immunotoxins in methods of treatment, and in view of the fact that a maytansinoid conjugated to an anti-ErbB2 antibody falls within the scope of a immunotoxin of Hudziak, and further in view of the fact that Lewis teaches that some tumors do not respond to anti-ErbB2 antibodies, one would have been motivated to use the antibodies of Hudziak to make the maytansinoid conjugates to the claimed methods because Hudziak teaches that ErbB2 (Her-2) is

amplified or overexpressed in many human malignancies (col. 2, lines 38-64) and because Lewis teaches that not all ErbB2 overexpressing tumors respond to anti-ErbB2 antibodies.

Applicants argue that the claimed inventions are free of the prior art because the prior art fails to teach methods comprising the active steps of determining whether a tumor overexpressed ErbB2 and also determining that the tumor does not respond or responds poorly to treatment with an anti-ErbB2 antibody. However, this argument is unpersuasive, because the prior art (by way of Lewis) teaches that certain tumors, despite exhibiting over-expression of ErbB2, did not respond to the murine monoclonal antibody 4D5 by an inhibition in growth; and also because the prior art contemplated the use of anti-ErbB2 antibodies for the purpose of making immunotoxins (Hudziak). In other words, the prior art recognized that an anti-ErbB2 antibody could be used for the purpose of delivering a cytotoxic moiety to a tumor, especially to tumors that do not respond to the ErbB2 antibody alone even though the tumor overexpresses ErbB2.

7. Claims 1, 2, 4, 5, 8-33, 38-41 and 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in view of Carter (U.S. Patent 6,054,297; issued Apr. 25, 2000; effective filing date Aug. 21, 1992) and further in view of Lewis (Lewis, G.D. et al, Cancer Immunol. Immunother. 37: 255-263, 1993; cited in the IDS).

The claimed inventions are drawn to methods employing antibody conjugates comprising humanized anti-ErbB2 antibodies, where the humanized antibodies are humanized 4D5 antibodies. The humanized 4D5 antibodies may be any of huMab4D5-1, huMab4D5-2,

huMab4D5-3, huMab4D5-3, huMab4D5-4, huMab4D5-5, huMab4D5-6, huMab4D5-7, and huMab4D5-8.

Chari and Lewis teach as set forth above in Section No. 6. Neither Chari nor Lewis teaches conjugates comprising a humanized 4D5 antibody and any of the named humanized 4D5 antibodies (huMab4D5-1, huMab4D5-2, huMab4D5-3, huMab4D5-3, huMab4D5-4, huMab4D5-5, huMab4D5-6, huMab4D5-7, and huMab4D5-8).

However, Carter teaches humanized 4D5 antibodies and teaches each of the species of named species (huMab4D5-1, huMab4D5-2, huMab4D5-3, huMab4D5-3, huMab4D5-4, huMab4D5-5, huMab4D5-6, huMab4D5-7, and huMab4D5-8) by the disclosure of how to make these antibodies (see col. 49, line 27-col. 53-23 and col. 13, lines 20-30). HuMab4D5-8 is a growth inhibitory and cytotoxic antibody. Carter also teaches the humanized 4D5 antibodies may be used as immunotoxins, where they are conjugated with a cytotoxic moiety (see col. 44, line 23- col. 45, line 30).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Chari and of Carter to make an immunotoxin for the purpose of treating patients having tumors that overexpress ErbB2. In view of the teachings of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid. In view of the fact that Carter clearly contemplated the use of immunotoxins in methods of treatment, and in view of the fact that a maytansinoid conjugated to an anti-ErbB2 antibody falls within the scope of a immunotoxin of Carter, and further in view of the fact that Lewis teaches that some tumors do not respond to anti-ErbB2

antibodies, one would have been motivated to use the antibodies of Carter to make the maytansinoid conjugates to the claimed methods because Carter teaches that ErbB2 (Her-2) is amplified or overexpressed in many human malignancies (col. 3, line 56- col. 4, line 19) and because Lewis teaches that not all ErbB2 overexpressing tumors respond to anti-ErbB2 antibodies.

8. Claims 1, 2, 4-6, 8-12, 14, 20-33 and 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in view of Bacus (U.S. Patent 5,514,554; issued May 7, 1996; filing date Oct. 7, 1993) and further in view of Lewis (Lewis, G.D. et al, Cancer Immunol. Immunother. 37: 255-263, 1993; cited in the IDS).

Chari and Lewis teach as set forth above in Section No. 6. Neither Chari nor Lewis teaches conjugates comprising an anti-ErbB2 antibody.

However, Bacus teaches anti-ErbB2 antibodies that are growth inhibitory, that induce cell death and that induce apoptosis (see Table I, col. 12) and teaches that such antibodies may be conjugated to cytotoxic moieties (col. 4, lines 1-14; col. 15, lines 29-45).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Chari and of Bacus to make an immunotoxin for the purpose of treating patients having tumors that overexpress ErbB2. In view of the teachings of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid. In view of the fact that Bacus clearly contemplated

the use of immunotoxins in methods of treatment, and in view of the fact that a maytansinoid conjugated to an anti-ErbB2 antibody falls within the scope of an immunotoxin of Bacus, and further in view of the fact that Lewis teaches that some tumors do not respond to anti-ErbB2 antibodies, one would have been motivated to use the antibodies of Bacus to make the maytansinoid conjugates to the claimed methods because Bacus teaches that ErbB2 (Her-2) is amplified or overexpressed in many human malignancies (col. 2, lines 32-35) and because Lewis teaches that not all ErbB2 overexpressing tumors respond to anti-ErbB2 antibodies.

9. Claims 1, 2, 8-14, and 20-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in view of Huston (U.S. Patent 5,877,305; issued Mar. 2, 1999; effective filing date Feb. 6, 1992) and further in view of Lewis (Lewis, G.D. et al, Cancer Immunol. Immunother. 37: 255-263, 1993; cited in the IDS).

Chari and Lewis teach as set forth above in Section No. 6. Neither Chari nor Lewis teaches conjugates comprising an anti-ErbB2 antibody (or anti-ErbB2 antibody fragments) and neither Chari nor Lewis teach methods for treatment of metastic breast cancer.

However, Huston teaches single-chain Fv comprising a binding site that binds to ErbB2 and methods of treatment of cancer comprising linking the single-chain Fv to a therapeutic agent, which is an agent that has the ability to limit the proliferation of a tumor cell (col. 1, lines 25-26; col. 5, lines 11-23; col. 8, lines 25-34). Huston also teaches methods for treatment of metastatic breast cancer (col. 1, lines 39-58 and col. 5, lines 51-63).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Chari and of Huston to make an immunotoxin for the purpose of treating patients having tumors that overexpress ErbB2. In view of the teachings of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid. In view of the fact that Huston clearly contemplated the use of single-chain Fv linked to a therapeutic agent in methods of treatment, and in view of the fact that a maytansinoid conjugated to an anti-ErbB2 antibody falls within the scope of a single-chain Fv linked to a therapeutic agent, and further in view of the fact that Lewis teaches that some tumors do not respond to anti-ErbB2 antibodies, one would have been motivated to use the antibodies of Huston to make the maytansinoid conjugates to the claimed methods because Huston teaches that ErbB2 (Her-2) is a tumor antigen (col. 2, lines 1-9) and because Lewis teaches that not all ErbB2 overexpressing tumors respond to anti-ErbB2 antibodies.

10. Claims 1, 2, 8-12, 22-33 and 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in view of King (U.S. Patent 5,747,261; issued May. 5, 1998; effective filing date Mar. 5, 1986) and further in view of Lewis (Lewis, G.D. et al, Cancer Immunol. Immunother. 37: 255-263, 1993; cited in the IDS).

Chari and Lewis teach as set forth above in Section No. 6. Neither Chari nor Lewis teaches conjugates comprising an anti-ErbB2 antibody (or anti-ErbB2 antibody fragments).

However, King teaches methods for treating cancer that express high levels of ErbB2 (mac117) comprising the administration of antibodies that bind the ErbB2, where the antibody is linked to one or more agents that will cause injury to cells for the purpose of directing the toxic agent to the cancer cells that over express ErbB2 (see col. 16, line 61 – col. 17 line 18).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Chari and of King to make an immunotoxin for the purpose of treating patients having tumors that overexpress ErbB2. In view of the teachings of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid. In view of the fact that King clearly contemplated the use of an antibody linked to one or more agents that will cause injury to cells in methods of treatment, and in view of the fact that a maytansinoid conjugated to an anti-ErbB2 antibody falls within the scope of an antibody linked to one or more agents that will cause injury to cells, and further in view of the fact that Lewis teaches that some tumors do not respond to anti-ErbB2 antibodies, one would have been motivated to use the antibodies of King to make the maytansinoid conjugates to the claimed methods because King teaches that ErbB2 (Her-2) is a tumor antigen that is overexpressed in some tumors (col. 15, lines 54-60) and because Lewis teaches that not all ErbB2 overexpressing tumors respond to anti-ErbB2 antibodies.

11. Claims 1, 34, 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (supra) in combination with Hudziak (supra), Baccus (supra), Huston (supra) or King

(supra), in view of Lewis (supra) as applied to claim 1 above, and further in view of Senger (U.S. Patent 6,022,541; issued 2/8/2000; effective filing 3/3/1997).

Claims 1, 34, 44 and 45 are drawn to methods of treatment comprising the administration of combinations of antibodies that bind to ErbB2, where at least one of the anti-ErbB2 antibodies is conjugated to a maytansinoid, and the second antibody may be conjugated to any cytotoxic agent, or also to a maytansinoid.

The combination of Chari with any of Hudziak (supra), Baccus (supra), Huston (supra) or King (supra), in view of Lewis (supra) fails to teach methods using combinations of at least two antibodies. However, the use of more than one antibody directed to the same antigen for the purpose of directing a cytotoxic moiety to a tumor cell is known in the art, as evidenced by the teachings of Senger. Senger teaches an improvement of immunological methods for tumor targeting, comprising the use of at least two antibodies where each of the antibodies that binds to vascular permeability factor (VPF; which binds to tumor endothelial cells) is conjugated to an effector moiety (col. 3, lines 12- 51), which may be toxin (col. 12, lines 46-57), and which may be the same or different for each of the two antibodies (col. 19, line 9 –col. 20, line 19). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the claimed inventions comprising the administration of combinations of antibodies, where the combination of Chari with either of Baccus, Huston or King and in view of Lewis suggests a method for the treatment of cancer overexpressing ErbB2, comprising the administration of a combination of antibodies that are maytansinoid-ErbB2 conjugates to tumors that do not respond to an ant-ErbB2 antibody alone, because Senger provides an example of a

treatment strategy where an antigen is targeted with two different antibodies, where each are conjugated to a toxin.

12. Claims 1, 34-37, 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (supra) in combination with Hudziak (supra), Baccus (supra), Huston (supra) or King (supra), in view of Lewis (supra) as applied to claim 1 above, and further in view of Sliwkowski (Sliwkowski, M.X. et al., J. Biol.Chem. 269: 14661-14665, 1994; IDS) or Carter (supra).

Claims 1, 34-37, 42 and 43 can be viewed as drawn to an embodiment of the invention where two anti-ErbB2 antibodies are used, one that is conjugated to a maytansinoid and is used only to target the maytansinoid to the tumor (and therefore, the first antibody by itself has no biological effect on the tumor); and the second one that is a biologically active antibody that inhibits the function of ErbB2 where the second antibody may be 2C4 or huMab4D5-8.

The combination of Chari with any of Hudziak (supra), Baccus (supra), Huston (supra) or King (supra), in view of Lewis (supra) fails to teach methods using a second anti-ErbB2 (or ErbB) antibody in combination with an anti-ErbB2-maytansinoid conjugate, where the second anti-ErbB2 antibody is 2C4 or huMab4D5-8. The two anti-ErbB2 antibodies, 2C4 and huMab4D5-8 (humanized version of murine 4D5) are known in the art as evidenced by the teachings of Sliwkowski (2C4) and Carter (huMab4D5-8). Sliwkowski teaches that 2C4 may be used to inhibit the binding of heregulin (a growth factor) to ErbB3 (page 14663, 1st col) and Carter teaches that huMab4D5-8 acts to recruit immune effector cells to a tumor (col. 54, lines 38-46). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a second antibody for the purposes of blocking the

effects of a growth factor such as heregulin, or for the purposes of recruiting immune effector cells to a tumor.

The methods of claims 1, 34-37, 42 and 43 can be viewed as a methods drawn to administering a combination of ingredients known in the art to be useful for the same purpose, i.e. an In re Kerkhoven analysis (In re Kerkhoven, 626, F.2s 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)). The court held that it is obvious to combine two compositions, in order to form a third composition, when each of the two compositions is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (MPEP 2144.06). In the instant case the first therapeutic composition is the anti-ErbB2-maytanisinoid conjugate (comprising an anti-ErbB2 antibody to which the tumor does not respond by reduction of growth), and the second therapeutic composition is an anti-ErbB2 antibody, such as 2C4 or huMab4D5-8, to which the tumor does respond by a reduction in growth.

13. Claims 1, 4-6, 8-19, 22-25, 27 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iwassa (U.S. Patent 5,217,713; issued Jun. 8, 1993; effective filing date Dec. 27, 1989) in combination with Carter (supra), Hudziak (supra), Baccus (supra), Huston (supra) or King (supra), in view of Lewis (supra).

The claimed inventions are interpreted to read on conjugates that comprise bispecific antibodies where one antigen binding site binds an ErbB2 tumor antigen and the second binding site binds a maytansinoid. This is interpretation is based on the fact that the specification fails to

provide a structural definition of the term "conjugate" and also in view of claim 27 that recites a "bispecific linker".

Iwassa teaches an immunocomplex that comprises a bispecific antibody that binds to a tumor antigen and binds to a maytansinoid (ansamitocin; see col. 4, lines 1-30; claim 1), thus targeting a maytansinoid to a tumor. Iwasa fails to teach that the immunoclomplex binds to the ErbB2 tumor antigen. However, any of Carter, Hudziak, Bacus, Huston or King teach that ErbB2 is a tumor antigen that is useful for targeting. Thus, the combination of Iwassa with any of Carter, Hudziak, Bacus, Huston or King provides a method of treating tumors with a bispecific antibody that comprises a binding portion that binds to ErbB2 and a second binding portion that binds to a maytansinoid. The combination of Iwassa with any of Carter, Hudziak, Bacus, Huston or King fails to teach targeting a population of patients that do not respond to an unconjugated anti-ErbB2 antibody.

Lewis teaches that some tumor cells overexpressing ErbB2 fail to respond to murine monoclonal antibody 4D5 by exhibiting growth inhibition (see page 261, 2nd col. To page 262, 1st col.).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Iwassa and any of Carter, Hudziak, Bacus, Huston or King to make an immunotoxin for the purpose of treating patients having tumors that overexpress ErbB2. In view of the teachings of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid. In view of the fact that any of Carter, Hudziak, Bacus, Huston or King clearly contemplated the use of an antibody

linked to one or more agents that will cause injury to cells in methods of treatment, and in view of the fact that a maytansinoid conjugated to an anti-ErbB2 antibody falls within the scope of an antibody linked to one or more agents that will cause injury to cells, and further in view of the fact that Lewis teaches that some tumors do not respond to the growth suppression effects of anti-ErbB2 antibodies, one would have been motivated to use the antibodies of Carter, Hudziak, Bacus, Huston or King to make the maytansinoid conjugates to the claimed methods for the purpose of delivering a cytotoxic moiety to ErbB2-expressing tumors.

14. Claims 1, 4-6, and 8-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4-6 and 14 are indefinite, because claim 1 recites that the claimed methods comprise a step of determining that the tumor does not respond, or responds poorly to treatment of an anti-ErbB2 antibody, whereas claims 4-6 and 14 recite that the antibody is characterized as "growth inhibitory", "induces cell death", or "induces apoptosis". Because the dependent claims to do not recite in which cells (e.g. specific reference cell line) the antibody is "growth inhibitory", "induces cell death", or "induces apoptosis", claim 1 is unclear in the recitation that "the tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody".

Claims 14 and 15 are further indefinite because of the recitation "monoclonal antibody 4D5" or "a 4D5 monoclonal antibody" absent a recitation of the ATCC number. The specification at page 20 defines "monoclonal antibody 4D5" or "4D5 monoclonal antibody" an antibody that has antigen binding residues of or derived from the murine 4D5 antibody.

Therefore, the definition does not supply any structural limits on the antibody used in the claimed methods because "has antigen binding residues" or "derived from" is open to interpretation and allows the interpretation that a "4D5 monoclonal antibody" may have almost nothing in common with the "4D5 (ATCC CRL 10463)" antibody that is referred to in the specification. Because the term "4D5 antibody" gives the appearance of referring to a specific and unique monoclonal antibody, given the definition supplied in the specification, the scope of the claims is unclear. This is especially the case for claim 15, which defines the antibody of the claimed methods in terms of binding to the same epitope as a "4D5 monoclonal antibody".

15. Claim 26 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the full scope of DM1 molecules is not adequately described, because the "R" group is not described.

Claim 26 is drawn to a method comprising administering an ErbB2 antibody-maytansinoid conjugate, where the maytansinoid is DM1 and has a structure as recited in claim 26. The structure depicted in claim 26 contains an R group, which is defined by the phrase "wherein R is capable of forming a chemical bond with a linker". The specification provides one example of "R", at page 7, line 12, where "R" is an SH group. The specification provides one example of linker, N-succinimidyl-4(2-pyridylthio)pentanoate to be used when "R" is an SH group. The one example of an R group and one example of a linker are not representative of the

broad species of possible groups that may be used to form a chemical bond with any member of the broad class of linkers. The examples of SH groups and N-succinimidyl-4(2-pyridylthio)pentanoate are not representative of the chemical genus of "R" and of the chemical genus of "linkers", because they do not define the full scope of the chemical genus of "R" or the chemical genus of "linkers". Therefore, the specification fails to describe the genus of "R" groups that are comprised by the formula for DM1, and consequently, the claimed methods are undescribed because a claim to a method using an inadequately described product is an inadequately described method.

Although the claims in the cases of University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. were drawn to DNA arts, the findings in these cases are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1, 2, 4, 5, 8-12, 14-17, 20-33, and 38-41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-18 of U.S. Patent No. 5,208,020 in view of in view of Hudziak (U.S. Patent 5,725,856; issued Mar. 10, 1998; effective filing date Jan. 12, 1988) and further in view of Lewis (Lewis, G.D. et al, Cancer Immunol. Immunother. 37: 255-263, 1993; cited in the IDS).

The claimed methods are an obvious species of the claims 13-18 of U.S. Patent No. 5,208,020 in view the teachings of Lewis, that some tumors respond poorly to unconjugated anti-ErbB2 antibodies when other tumors respond well to the same antibodies despite overexpression of ErbB2, and in view of the fact that Hudziak clearly contemplated the use of anti-ErbB2 antibody-based immunotoxins in methods of treatment. A maytansinoid conjugated to an anti-ErbB2 antibody falls within the scope of an anti-ErbB2 immunotoxin of Hudziak. One would have been motivated to use the antibodies of Hudziak to make the maytansinoid conjugates to the claimed methods because Hudziak teaches that ErbB2 (Her-2) is amplified or overexpressed in many human malignancies (col. 2, lines 38-54) and because Lewis teaches that not all ErbB2 overexpressing tumors respond to unconjugated anti-ErbB2 antibodies.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

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March 22, 2004

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